Patent
Attorney Docket No. CMED.10023

**IN THE UNITED STATES PATENT AND TRADEMARK OFFICE**

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| Inventor(s): Jerry Y. JONN et al. | Mail Stop: Amendment |
| Application No.: 09/919,877 | Group Art Unit: 1616 |
| Filing or 371(c) Date: August 2, 2001 | Examiner: Frank I. Choi |
| Title: Absorbable Adhesive Compositions | Confirmation No.: 4857 |

**RESPONSE UNDER 37 CFR § 41.37(d) TO NOTICE OF NON-COMPLIANT APPEAL BRIEF**

Mail Stop Amendment
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

In response to the Notice of Non-Compliant Appeal Brief mailed May 15, 2008, Appellant submits the following corrected Brief.

**Remarks** begin on page 2 of this paper.

## REMARKS

Sections VII.A and VIII have been amended in response to the Notice of Non-Compliant Appeal Brief mailed May 15, 2008. Although the evidence allegedly not contained in the original Brief consists of U.S. patents and therefore judicial notice should be taken of the contents therein, Appellant has removed from Section VII.A the references to U.S. Patent Nos. 4,579,891; 5,929,159; 7,048,913 and 7,125,571. Further, as requested in the Notice, the claim status identifiers and cancelled claims have been removed from the Claims Appendix (Section VIII).

If any questions remain, the Examiner is invited to contact the undersigned at the number given below.

Respectfully submitted,

HUTCHISON LAW GROUP PLLC

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## I. REAL PARTY IN INTEREST

Appellant respectfully submits that the assignee, Closure Medical Corporation, is the real party in interest.

## II. RELATED APPEALS AND INTERFERENCES

Upon information and belief, no other proceedings are known to Appellant, Appellant's legal representative, or the Assignee, which may be related to, directly affect or be directly affected by or have a bearing on the Board's decision in the pending appeal.

## III. STATUS OF CLAIMS

Claims 74-93 and 95-102 are pending and rejected in the present application, of which claim 74 is presented in independent form. Claims 1-73, 94 and 103-133 have been cancelled. Claims 74-93 and 95-102 were finally rejected in the Office Action mailed October 16, 2006. Accordingly, claims 74-93 and 95-102 are appealed and all applied rejections concerning those claims are herein being appealed.

## IV. STATUS OF AMENDMENTS

No amendment was filed subsequent to the final rejection issued October 16, 2007. All previous amendments have been entered.

## V. SUMMARY OF CLAIMED SUBJECT MATTER

The claimed subject matter of independent claim 74 relates to a biocompatible adhesive composition comprising a first monomer species, a second monomer species and a polymerization initiator or accelerator. *Specification, page 3, line 32 – page 4, line 2; page 4, lines 5-6.* The first monomer species comprises an alkyl ester cyanoacrylate. *Specification, page 3, line 33.* The second monomer species is different from the first monomer species and comprises an alkyl α-cyanoacrylate. *Specification, page 7, lines 2-5.*

The polymerization initiator or accelerator comprises a quaternary amine. *Specification, page 4, lines 2-4.* The first monomer species has a first polymer absorption rate and the second monomer species has a second polymer absorption rate different from the first polymer absorption rate and the biocompatible adhesive composition has a third polymer absorption rate different from the first and second polymer absorption rates. *Specification, page 10, lines 7-22.*

Dependent claim 75 is directed to a biocompatible adhesive composition wherein the first monomer species and the second monomer species have different polymer absorption rates such that a polymer absorption rate of a faster absorbing monomer species is at least 10% faster than a polymer absorption rate of a slower absorbing monomer species. *Page 10, lines 22-24.*

Dependent claim 87 is directed to a biocompatible adhesive composition wherein the composition comprises a monomer blend comprising from about 25 to about 40 parts by weight butyl lactoyl cyanoacrylate and from about 60 to about 75 parts by weight octyl cyanoacrylate, at least one anionic stabilizer and at least one radical stabilizer. Dependent claim 88 is directed to a biocompatible adhesive composition wherein the anionic stabilizer comprises about 25 to about 100 ppm of sulfuric acid and from about 1 to about 50 ppm sulfur dioxide, and the radical stabilizer comprises from about 100 to about 2000 ppm hydroquinone, from about 10 to about 200 ppm p-methoxyphenol, and from about 100 to about 10,000 ppm butylated hydroxyanisole. *Page 23, lines 12-22.*

Dependent claim 92 is directed to a biocompatible adhesive composition further comprising about 20 ppm sulfuric acid, 0 to 20 ppm sulfur dioxide, 0 to 2000 ppm hydroquinone, 0 to 180 p-methoxyphenol and 0 to 2000 ppm butylated hydroxyanisole. Dependent claim 93 is directed to the biocompatible adhesive composition of claim 92, wherein the first monomer species comprises butyl lactoyl cyanoacrylate and the second monomer species comprises octyl α-cyanoacrylate. *Page 24, line 27 – page 25, line 3.*

Dependent claim 99 is directed to a biocompatible adhesive composition wherein the polymerization initiator or accelerator polymerizes a mixture of the first monomer species and the second monomer species in less than 3 minutes. *Page 13, lines 13-15.*

## VI. GROUNDS OF REJECTION TO BE REVIEWED ON APPEAL

1. Whether claims 89-91 are unpatentable under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

2. Whether claims 74-93 and 95-102 are unpatentable under 35 U.S.C. § 103(a) over Clark et al., U.S. Patent No. 5,981,621, in view of Kronenthal et al., U.S. Patent No. 3,995,641, Hammerslag, U.S. Patent No. 6,386,203, and EP 0 965 623.

3. Whether claims 74-93 and 95-102 are unpatentable under 35 U.S.C. § 103(a) over Clark et al., U.S. Patent No. 5,981,621, in view of Kronenthal et al., U.S. Patent No. 3,995,641, Hammerslag, U.S. Patent No. 6,386,203, and EP 0 965 623, in further view of Banitt et al., U.S. Patent No. 3,559,652, and Collins (Arch. Surg. 93:428-432 (1966)).

4. Whether claims 74-93 and 95-102 are unpatentable under 35 U.S.C. § 103(a) over Berger et al., U.S. Patent No. 5,998,472, in view of Kronenthal et al., U.S. Patent No. 3,995,641, Hammerslag, U.S. Patent No. 6,386,203, and Clark et al., U.S. Patent No. 5,981,621.

## VII. ARGUMENT

### A. Claims 89-91 Are Not Indefinite under 35 U.S.C. § 112, second paragraph

In the final Office Action, the Examiner rejected claims 89-91 under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The Examiner stated: "...the claims indicate that the composition contains at least one additive but then indicates that the amount of the additive can be "up to " the claimed amount which renders the claim ambiguous." *Office Action mailed October 16, 2006, page 2.* The Examiner further stated, "As such, the amendment from "0" to "up to" does not change the fact that the claim still requires the presence of an ingredient and then indicates that it contains 0% of the ingredient." *Office Action mailed October 16, 2006, page 2.* Appellant disagrees for the following reasons.

Claims 89-91 are dependent claims which read as follows:

89. The biocompatible adhesive composition of claim 86, wherein said composition further comprises at least one additive selected from the group consisting of anionic stabilizing agents, free radical stabilizing agents and plasticizers, and the additive is present in an amount of up to 25 weight % based on a total weight of the composition.

90. The biocompatible adhesive composition of claim 86, wherein said composition further comprises at least one additive selected from the group consisting of anionic stabilizing agents, free radical stabilizing agents and plasticizers, and the additive is present in an amount of up to 10 weight % based on a total weight of the composition.

91. The biocompatible adhesive composition of claim 86, wherein said composition further comprises at least one additive selected from the group consisting of anionic stabilizing agents, free radical stabilizing agents and plasticizers, and the additive is present in an amount of up to 5 weight % based on a total weight of the composition.

Each claim requires that the composition comprises at least one additive selected from a particular group. Each claim requires that the additive is present in an amount up to a particular amount. One of ordinary skill in the art would readily understand that an additive as claimed is present in the composition in an amount of not more than the amount claimed.

According to 35 U.S.C. § 112, second paragraph:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

The primary purpose of this requirement of definiteness of claim language is to ensure that the scope of the claims is clear so the public is informed of the boundaries of what constitutes infringement of the patent. *MPEP § 2173.*

As described above, the Examiner has objected to the language of these claims as requiring the presence of an ingredient and then indicating that the composition contains 0% of the ingredient. However, this argument does not make sense on its face. If the claim, as the Examiner states, requires the presence of an ingredient, the ingredient must be present. Moreover, the claims do not state that there is 0% of the ingredient; rather, the claims recite that the amount of the additive may be "up to" a particular amount. Thus, the claims require

both that (1) an additive is present and that the additive is (2) in an amount up to the amount as claimed.

Appellant acknowledges the case cited by the Examiner, *In re Mochel*, 470 F.2d 638 (CCPA 1974). However, as stated in the MPEP, "[s]ome terms have been determined to have the following meanings *in the factual situations of the reported cases*: the term "up to" includes zero as a lower limit...", citing *In re Mochel (emphasis added). MPEP § 2173.05(c)*. However, the language "up to" for an amount also has been used and accepted in a large number of patents issued after the date of the case cited by the examiner.

In the present factual situation, the rejected claims include two recitations or features. First, the composition further comprises at least one additive selected from the group consisting of anionic stabilizing agents, free radical stabilizing agents and plasticizers. Second, the rejected claims require that the additive is present in a particular amount. Thus, the claims inform the public of the boundaries of what constitutes infringement of the patent – first, that an additive as claimed is present and second, the additive is present in an amount up to the amount claimed. In view of the recitations of the claims which require both that there is an additive and that the additive is present in an amount as claimed, the rejected claims are both clear and definite. Thus, Appellant respectfully requests that this rejection be reversed.

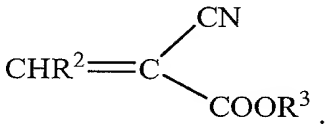
**B. Claims 74-93 and 95-102 are patentable under 35 U.S.C. § 103(a) over Clark et al., U.S. Patent No. 5,981,621, in view of Kronenthal et al., U.S. Patent No. 3,995,641, Hammerslag, U.S. Patent No. 6,386,203, and EP 0 965 623**

**1. The Cited Art**

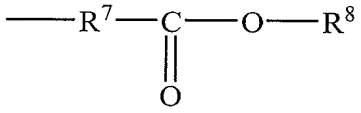
**a. U.S. Patent No. 5,981,621 to Clark et al.**

U.S. Patent No. 5,981,621 to Clark et al. (hereinafter "Clark") discloses a wound closure monomer composition comprising (A) at least one monomer, which forms a medically acceptable wound closure polymer, (B) at least one plasticizing agent, and (C) at least one acidic stabilizing agent. *Column 2, line 64 - column 3, line 2.* Clark describes the monomers that may be used as polymerizable monomers, e.g., anionically polymerizable or free radical polymerizable. *Column 3, lines 52-54.* Examples of monomers within the scope

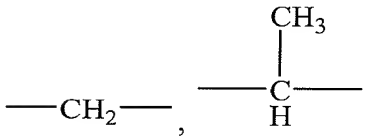
of a formula of useful 1,1-disubstituted ethylene monomers as shown include alpha-cyanoacrylates, vinylidene cyanides, $C_1$-$C_4$ alkyl homologues of vinylidene cyanides, dialkyl methylene malonates, acylacrylonitriles, vinyl sulfinates and vinyl sulfonates of particular formulas. *Column 4, lines 1-7.* Clark states that preferred monomers have the formula



As disclosed, $R^2$ is hydrogen and $R^3$ may be, among other things, a group having the formula



wherein $R^7$ is



, or $-C(CH_3)_2-$, and $R^8$ is an organic radical. *Column 4, lines 7-35.*

Claim 10 of Clark recites a composition of claim 1 wherein the composition comprises at least two different monomers. Clark also discloses that initiators that initiate polymerization and/or cross-linking of the material may be applied to a surface portion or to the entire surface of the applicator tip, including the interior and the exterior of the tip, and that the suitable initiators include, among others, cationic surfactants such as benzalkonium chloride. *Column 11, lines 18-67.*

**b. U.S. Patent No. 3,995,641 to Kronenthal et al.**

U.S. Patent No. 3,995,641 to Kronenthal et al. (hereinafter "Kronenthal") discloses carbalkoxyalkyl 2-cyanoacrylates. *Abstract.* Monomeric carbalkoxyalkyl 2-cyanoacrylates may be employed individually or as comonomers in biological adhesive compositions. *Column 2, lines 5-7.* As stated in the Description of the Prior Art, an object of the Kronenthal invention "is to provide cyanoacrylate monomers which can be used either alone

or as comonomers in the bonding of similar or dissimilar materials without the use of heat or catalyst during the bonding operation. Comonomer compositions are of interest for specific uses because they may provide advantageous combinations of properties not completely embodied in individual monomers." *Column 1, lines 44-51.*

Kronenthal describes alkyl 2-cyanoacrylates as having failed to have the required properties of low toxicity and adequate absorption by the tissues. The Kronenthal specification states that methyl 2-cyanoacrylate gives rise to a severe inflammatory response at the site of application and the n-butyl and isobutyl 2-cyanoacrylate monomers are not absorbed well (if at all) by the tissues. *Column 1, lines 14-33.*

**c. U.S. Patent No. 6,386,203 to Hammerslag**

U.S. Patent No. 6,386,203 to Hammerslag (hereinafter "Hammerslag") discloses methods and compositions for closing and sealing a wound, laceration, incision, or other percutaneous opening using an adhesive. Preferred sealing media comprise cyanoacrylates combined with fumed silica. *Abstract.* According to Hammerslag, formulations of sealing media preferably comprise a tissue adhesive such as a cyanoacrylate which has been modified to increase its viscosity and, preferably decrease its polymerization rate. *Column 5, lines 7-10.* Hammerslag additionally states:

> Examples of adhesive compounds include cyanoacrylates and fibrin based adhesives. Polymerizable cyanoacrylates that have been cross-linked or co-polymerized with other compounds that may alter elasticity, modify viscosity, aid biodegradation or change some other property of the resulting material may also be used as adhesive compounds in accordance with the present invention. For example, polyacrylic acid having a molecular weight of 200,000 to 600,000 may be cross-linked to a cyanoacrylate to form compounds which may allow the absorbability to be coordinated with the tissue regeneration rate and may feature higher elasticity than cyanoacrylates alone. Absorbability is unnecessary for topical applications, in which the adhesive film will simply fall off in a few days.

*Column 5, lines 22-34 (emphasis added).*

**d. EP 0 965 623 to Malofsky et al.**

EP 0 965 623 (hereinafter "EP '623") discloses an adhesive composition including a polymerizable adhesive monomer, at least one vapor phase stabilizer, and at least one liquid phase stabilizer. *Abstract.* The monomer may be a cyanoacrylate. Claim 5 recites that the monomer is at least one member selected from the group consisting of n-butyl cyanoacrylate, 2-octyl cyanoacrylate, ethyl cyanoacrylate, methyl cyanoacrylate, ethoxyethyl cyanoacrylate, and methoxyethyl cyanoacrylate. No specific combinations of monomers are described.

**2. Claims 74, 76-86, 89-91, 95-98 and 100-102**

Claim 74 is directed to a biocompatible adhesive composition comprising a first monomer species comprising an alkyl ester cyanoacrylate, a second monomer species different from the first monomer species comprising an alkyl α-cyanoacrylate, and a polymerization initiator or accelerator comprising a quaternary amine. The first and second monomer species have different polymer absorption rates and the biocompatible adhesive composition has a third polymer absorption rate different than the polymer absorption rates of the monomer species.

The mixture of at least two different monomer species where the different monomer species have different polymer absorption rates allows for adjustment and tailoring of the degradation rate of the resultant formed polymer. *Specification, page 4, lines 5-13.* The selection of monomer will affect the absorption rate of the resultant polymer, as well as the polymerization rate of the monomer. Two or more different monomers that have varied absorption and/or polymerization rates may be used in combination to give a greater degree of control over the absorption rate of the resultant polymer, as well as the polymerization rate of the monomer. The selection of the monomer and initiator as taught in the specification provide control within relatively narrow and predictable ranges for both the polymerization and absorption rates. *Specification, page 10, lines 7-14.* As described in the specification, for example:

> Some alkyl ester cyanoacrylate monomers may react slowly due to bulky alkyl groups, apparently limiting their applicability as surgical adhesives. By themselves, alkyl ester cyanoacrylates cure in several hours, or in some cases, do not fully cure at all. To overcome problems associated with

> slow polymerization of the monomers, a compatible agent which initiates or accelerates polymerization of the alkyl ester cyanoacrylate monomer, may be used with the monomer composition. Initiators and accelerators particularly suitable for use with alkyl ester cyanoacrylates provide a fast cure rate while retaining the absorbable properties of the adhesive. Alkyl ester cyanoacrylates stimulated to cure by a suitable initiator or accelerator may be made to cure in as short as a few seconds to a few minutes. The cure rate may be closely controlled by selection of an amount or concentration of initiator or accelerator added to the cyanoacrylate and may thus be readily controlled by one skilled in the art in the light of the present disclosure. A suitable initiator provides a consistent controllable complete polymerization of the monomer so that the polymerization of the monomer can be made to occur in the time desired for the particular application. Quaternary amine initiators or accelerators are particularly desirable with alkyl ester cyanoacrylate monomers for such reasons.

*Specification, page 12, lines 13-29.*

Claims 76 and 77 depend directly or indirectly on claim 74 and are directed to compositions wherein the alkyl ester cyanoacrylate has a particular formula. *Page 6, lines 1-4*; *page 8, lines 21-22*. Claim 78 is dependent on claim 74 and is directed to a biocompatible adhesive composition wherein the alkyl ester cyanoacrylate is selected from the group consisting of butyl lactoyl cyanoacrylate, butyl glycoloyl cyanoacrylate, isopropyl glycoloyl cyanoacrylate, ethyl lactoyl cyanoacrylate, and ethyl glycoloyl cyanoacrylate. *Page 9, lines 1-4*.

Claim 79 is dependent on claim 74 and is directed to a biocompatible adhesive composition wherein the second monomer species is an alkyl α-cyanoacrylate having an alkyl group of from about 2 to about 12 carbon atoms. *Page 11, line 11*. Claim 80 is dependent on claim 79 and is directed to a biocompatible adhesive composition wherein the second monomer species is selected from the group consisting of octyl α-cyanoacrylate, hexyl α-cyanoacrylate, butyl α-cyanoacrylate and ethyl α-cyanoacrylate.

Claims 81-84 are dependent on claim 74 and recite particular weight ratios of the first monomer species to the second monomer species. Claim 85 is dependent on claim 74 and is directed to a biocompatible adhesive composition wherein the first monomer species comprises butyl lactoyl cyanoacrylate and the second monomer species comprises octyl α-cyanoacrylate.

Claim 86 is dependent on claim 74 and recites that the biocompatible adhesive composition further comprises at least one additive selected from the group consisting of anionic stabilizing agents, free radical stabilizing agents, colorants, and plasticizers. Claims 89-91 are dependent on claim 86 and recite that the compositions further comprise at least one additive selected from the groups consisting of anionic stabilizing agents, free radical stabilizing agents and plasticizers, and the additive is present in a particular amount.

Claims 95-98 are dependent on claim 74 and recite various features relating to the polymerization initiator or accelerator. Claim 100 is dependent on claim 74 and recites that the first monomer species and the second monomer species are present in an amount of at least 65 percent by weight of the biocompatible adhesive composition. Claim 101 is dependent on claim 74 and recites that at least the first monomer species forms a polymer that is absorbable. Claim 102 is directed to a polymerized film formed by curing the biocompatible adhesive composition of claim 74.

Obviousness depends on four factors: (1) the scope and content of the prior art; (2) the differences between the claimed invention and the prior art; (3) the level of ordinary skill in the art; and (4) any relevant secondary considerations. *Dystar Textilfarben GmbH & Co. Deutschland KG v. C.H. Patrick Co.,* 464 F.3d 1356, 1360, 80 USPQ2d 1641 (Fed. Cir. 2006), citing *Graham v. John Deere Co.,* 383 U.S. 1, 17 (1966). The Court of Appeals for the Federal Circuit has articulated a subsidiary requirement for the first Graham factor which requires that where the claim limitations are found in a number of prior art references, the fact finder must determine what the prior art teaches, whether it teaches away from the claimed invention, and whether it motivates a combination of teachings from different references. 464 F.3d at 1360. To establish a *prima facie* case of obviousness based on a combination of elements in the prior art, the law requires a motivation to select the references and to combine them in the particular claimed manner to reach the claimed invention. *Eli Lilly and Co. v. Zenith Goldline Pharmaceuticals, Inc.*, 471 F.3d 1369, 1379, 81 USPQ2d 1324 (Fed. Cir. 2006).

As set forth in the Manual on Patent Examining Procedure, to establish a *prima facie* case of obviousness, three basic criteria must be met. First, there must some suggestion or motivation, either in the references themselves or in the knowledge in the art, to modify the

reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the cited art reference or references when combined must teach or suggest all the claim limitations. *See MPEP § 2143.* The foregoing criteria for a *prima facie* case of obviousness have not been met.

For this rejection, the Examiner has cited four patents in combination. The scope and content of the art is discussed above and within the argument as presented below, which also describes the differences between the cited art and the invention as defined in the rejected claims. The level of ordinary skill in the art has not been particularly addressed by the Examiner.

As specifically stated by the Examiner, at least one difference between the prior art and the claimed invention is that the cited art does not expressly disclose a composition or film having a first monomer, which includes alkyl ester cyanoacrylate, and a different second monomer where the absorption rate of the first monomer species is different from the absorption rate of the second monomer species. *Office Action mailed October 16, 2006, page 4.* However, the Examiner relies on Clark for the combination of monomers claimed:

> Contrary to Applicant's arguments Clark et al. as indicated above does disclose the use of an alkyl ester and alkyl alpha cyanoacrylate as it specifically incorporates by reference the US Patent, Kronenthal et al, and identifies the use of 2-octyl cyanoacrylate which is an alkyl alpha cyanoacrylate.

*Office Action mailed October 16, 2006, page 5.* This interpretation is in error; Clark, alone, or in combination with Kronenthal, does not include any disclosure, suggestion or motivation to combine a first monomer species comprising an alkyl ester cyanoacrylate and a second monomer species different from the first monomer species comprising an alkyl α-cyanoacrylate and a polymerization initiator or accelerator comprising a quaternary amine.

Clark claims a composition comprising at least two different monomers but does not provide any disclosure or suggestion as to which different monomers should be used. The monomers listed in Clark include both cyanoacrylate monomers and other types of monomers. *Column 3, line 61 – column 4, line 7.* Incorporation by reference to Kronenthal does not remedy this lack of disclosure in Clark since Kronenthal only suggests comonomers of carbalkoxyalkyl 2-cyanoacrylate monomers. The mere identification of the use of 2-octyl

cyanoacrylate among the monomers disclosed in Clark does not provide the requisite motivation to combine that particular cyanoacrylate monomer with an alkyl ester cyanoacrylate monomer as asserted by the Examiner. *See, In re Fine,* 837 F.2d 1071, 1075 (Fed. Cir. 1988) ("One cannot use hindsight reconstruction to pick and choose among isolated disclosures in the prior art to deprecate the claimed invention.").

Moreover, no suggestion or motivation to modify the teachings of the cited art has been provided. The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art and not based on applicant's disclosure. *In re Vaeck*, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991). No suggestion of the combination as claimed is found in the cited art or a combination thereof. In addition, no suggestion to modify the disclosures of the cited art to provide the combination of monomers and initiator or accelerator as claimed is found in the art.

Clark discloses a wound closure monomer composition. Claim 10 of Clark recites a composition wherein the composition comprises at least two different monomers, but there is no disclosure in Clark as to what those monomers should be. Clark does not describe any use of particular combinations of monomers for purposes of absorbability, and does not describe or suggest the particular combination of monomers defined in the rejected claims or those monomers with a polymerization initiator or accelerator comprising a quaternary amine.

Kronenthal is directed to carbalkoxyalkyl cyanoacrylates which are absorbable in mammalian tissue. Kronenthal states that alkyl 2-cyanoacrylates are not absorbed well. Initiators are not disclosed.

Hammerslag does not describe or suggest the use of any combination of cyanoacrylate monomers. Rather, Hammerslag suggests the use of polymerizable cyanoacrylates that have been cross-linked or co-polymerized with other compounds. The only example given is a non-cyanoacrylate compound, polyacrylic acid.

Hammerslag further states that there is a wide variation in rates and facility of in vivo biodegradation of members of the cyanoacrylate family and describes the differences including indicating that it is within the abilities of one of skill in the art to use information in the literature along with routine experimentation to choose a member of the cyanoacrylate family with suitable biodegradation characteristics. Nothing in the disclosure of Hammerslag

suggests combining different cyanoacrylate monomers as claimed. Initiators are only generally mentioned.

EP '623 includes a claim which is directed to at least one member of certain specific cyanoacrylate monomers. None of these monomers is an alkyl ester cyanoacrylate. Moreover, EP '623 does not disclose or suggest that any combination of monomers would provide advantages in absorbability.

According to the Examiner, the references in combination suggest selecting the claimed monomers and the reasoning to do so because (1) Kronenthal suggests that alkyl ester cyanoacrylates are more biodegradable than alkyl alpha cyanoacrylates having chains at least as long as isobutyl, (2) one of ordinary skill in the art reading Hammerslag in view of Kronenthal and Clark would expect that the substance which can be used to obtain desired biodegradation rates can be another cyanoacrylate, and (3) EP '623 is not limited to the cyanoacrylates listed as it cites to Kronenthal. *Office Action mailed October 16, 2006.* None of these factors would have led one of ordinary skill in the art to the invention as defined in the rejected claims.

Kronenthal includes examples of the biodegradation of the carbalkoxyalkyl 2-cyanoacrylates described therein compared to alkyl 2-cyanoacrylates and states, "It is apparent from the above data that the cyanoacrylates of the instant invention [carbalkoxyalkyl cyanoacrylates] demonstrate good in vivo absorbability, ..." *Column 13, lines 28-29.* The table referred to shows that isobutyl 2-cyanoacrylate was unchanged [did not disintegrate]. *Column 13, lines 15-25.* Thus, the Examiner's assertion that Kronenthal suggests that alkyl ester cyanoacrylates are more biodegradable than alkyl alpha cyanoacrylates having chains at least as long as isobutyl is correct. However, this fact does not lead to the combination of alkyl ester cyanoacrylates and alkyl α-cyanoacrylates with a polymerization initiator or accelerator comprising a quaternary amine as claimed. First, Kronenthal only teaches comonomers of carbalkoxyalkyl 2-cyanoacrylates, not combinations of different species of cyanoacrylate monomers. Second, one of skill in the art would actually be led by Kronenthal away from the use of alkyl 2-cyanoacrylates as Kronenthal's examples show the lack of biodegradability of a longer chain homolog (isobutyl 2-cyanoacrylate) and the histotoxicity of a shorter chain homolog of alkyl 2-cyanoacrylate

(methyl 2-cyanoacrylate). A prior art reference must be considered in its entirety, i.e., as a whole, including portions that would lead away from the claimed invention. *W.L. Gore & Associates, Inc. v. Garlock, Inc.*, 721 F.2d 1540, 220 USPQ 303 (Fed. Cir. 1983), cert. denied, 469 U.S. 851 (1984).

The Examiner further asserts that one of ordinary skill in the art reading Hammerslag in view of Kronenthal and Clark would expect that the substance which can be used to obtain desired biodegradation rates can be another cyanoacrylate. However, Hammerslag describes that a polymerizable cyanoacrylate may be cross-linked or co-polymerized with other compounds that may alter biodegradation. The only example given is polyacrylic acid. *Column 5, lines 22-34.* Kronenthal, as noted, shows advantages of carbalkoxyalkyl 2-cyanoacrylates and disadvantages of alkyl 2-cyanoacrylates, not combinations thereof. Clark does not refer to or provide any suggestion regarding the degradation or absorbability of particular cyanoacrylate polymers and merely claims combinations of monomers generally. Thus, the asserted motivation to combine the art as asserted by the Examiner is in error.

As to allegation (3) of the Examiner ("EP '623 is not limited to the cyanoacrylates listed as it cites to Kronenthal"), this assertion does not provide the requisite motivation to combine the teachings of the cited art. EP '623 specifies that the monomer is at least one member selected from a group of six compounds. No specific combinations are shown. Moreover, two of the six compounds (n-butyl cyanoacrylate and methyl cyanoacrylate) are specifically identified in Kronenthal as having histotoxicity or poor biodegradation properties. Thus, the citation to Kronenthal does not add to the disclosure of EP '623 since Kronenthal teaches away from the use of the alkyl 2-cyanoacrylates as listed in EP '623.

In view of the foregoing, the combination of cited art would not have suggested the invention as defined in the rejected claims. None of the cited art, even in combination, provides suggestion regarding the advantages of the claimed combination of monomers and polymerization accelerator or initiator. The combination of a faster absorbing monomer species and non-absorbable (or less absorbable or slower absorbing) monomer species allows for adjustment and tailoring of the degradation rate of the resultant formed polymer. *Page 4, lines 11-13.* The selection of monomer will affect the absorption rate of the resultant polymer, as well as the polymerization rate of the monomer. Two or more different

monomers that have varied absorption and/or polymerization rates may be used in combination to give a greater degree of control over the absorption rate of the resultant polymer, as well as the polymerization rate of the monomer. Thus, an important aspect lies in the selection of the monomer and initiator to control within relatively narrow and predictable ranges both the polymerization and absorption rates. *Page 10, lines 7-14.*

None of the foregoing features are taught or suggested by the cited art, alone or in combination. Clark and EP '623 do not include any information regarding combinations of monomers for characteristics of absorbability. Kronenthal describes degradation with respect only to carbalkoxyalkyl cyanoacrylates and the advantages of carbalkoxyalkyl cyanoacrylates over alkyl 2-cyanoacrylates. *Column 13 , lines 1-65.* Hammerslag only refers to biodegradation in terms of different members of the cyanoacrylate family (not with regard to combinations of cyanoacrylates (*column 6, lines 32-48)*) or with regard to a combination of a cyanoacrylate and another compound (*column 5, lines 23-34*).

The Office Action states that is would have been well within the skill of one of ordinary skill in the art to make the combination as claimed. *Office Action mailed October 16, 2007, page 4.* However, such a statement is not sufficient to establish a prima facie case of obviousness without some objective reason to combine and/or modify the teachings of the cited art. *See, MPEP § 2143.01 IV*; *Ex parte Levengood*, 28 USPQ2d 1300 (BPAI 1993). Particular findings must be made as to the reason the skilled artisan, *with no knowledge of the claimed invention*, would have selected the monomers claimed in combination with an initiator or accelerator comprising a quaternary amine for the invention as defined in the rejected claims. *In re Kotzab*, 217 F.3d 1365, 55 USPQ2d 1313 (Fed. Cir. 2000) (No finding as to the specific understanding or principle within the knowledge of a skilled artisan that would have motivated one with no knowledge of Kotzab's invention to make the combination in the manner claimed.). No such reason has been provided. The cited art does not discuss or even acknowledge the problem of selecting cyanoacrylate monomer species with different absorption rates and initiators or accelerators for use therefore such that polymerization of the combination will provide an adhesive composition with an absorption rate different from either of the monomers.

Given this lack of disclosure or suggestion, one of ordinary skill in the art would not

have had any expectation of success in the use of the claimed combination. Clark and EP '623 do not contain any disclosure regarding a combination of particular monomers for absorbability. Hammerslag mentions the wide variation in the rates and facility of in vivo biodegradation of polymers made from monomers which may be used as adhesive compounds, specifically noting the wide variation in such rates among the members of the cyanoacrylate family. Hammerslag states:

> There are several studies of biodegradation rates of polymers formed by various members of the cyanoacrylate family in the scientific and medical literature. It is within the abilities of one of skill in the art to use such information in the literature along with routine experimentation in order to choose a member of the cyanoacrylate family with suitable biodegradation characteristics for use in accordance with the present invention.

*Column 6, lines 48-56.* Hammerslag does not teach or suggest a combination of cyanoacrylate monomers nor provide any information regarding the polymerization kinetics which may be involved with such a combination. As pointed out in the present specification, the selection of monomer will affect the absorption rate of the resultant polymer, as well as the polymerization rate of the monomer. Since Hammerslag does not teach or suggest combinations of cyanoacrylates, Hammerslag also did not recognize the issue regarding polymerization rate.

Kronenthal is specifically directed to providing cyanoacrylate monomers with properties superior to those found with the alkyl 2-cyanoacrylates. *Column 1, lines 14-36.* The examples compare methyl 2-cyanoacrylate, isobutyl 2-cyanoacrylate, carbethoxymethyl 2-cyanoacrylate, carbo-i-butoxymethyl 2-cyanoacrylate and carboctoxymethyl 2-cyanoacrylate in terms of hydrolytic stability, bond strength, microcalorimetry tests, degradation tests and tissue reaction tests. *Column 11, line 23 – column 13, line 65.* The isobutyl 2-cyanoacrylate did not show adequate absorbability while the methyl 2-cyanoacrylate showed significant inflammation indicating histotoxicity. Kronenthal states that the data illustrate that the carboalkyoxyalkyl cyanoacrylates of the inventions are generally well suited as absorbable tissue adhesives and demonstrate certain functional advantages over the isobutyl 2-cyanoacrylate of the prior art, particularly in regard to high absorbability associated with a low order of tissue reaction. *Column 13, lines 59-65.* Thus,

Kronenthal shows the advantages of carbalkoxyalkyl cyanoacrylates over alkyl cyanoacrylates, but lacks any disclosure or suggestion regarding combinations of monomers or polymerization rate issues involved therewith.

In view of the foregoing, one of ordinary skill in the art attempting to prepare a biocompatible adhesive composition with the advantages as described in the present specification would not have obtained the requisite knowledge from the combination of art cited by the examiner to have a reasonable expectation of success.

The final requirement for a prima facie case of obviousness is that all the claim limitations must be taught or suggested by the prior art. From the foregoing, it is clear that not every element of the invention has been taught. Rather, the cited documents lack any teaching or suggestion regarding a combination of monomers as claimed, wherein the first monomer species has a first polymer absorption rate, and the second monomer species has a second polymer absorption rate different from the first polymer absorption rate, and the biocompatible adhesive composition has a third polymer absorption rate different from the first and second polymer absorption rates. In addition, none of the cited art discloses or suggests the combination of a monomer species comprising an alkyl ester cyanoacrylate and a monomer species comprising an alkyl α-cyanoacrylate with an initiator or accelerator comprising a quaternary amine.

The Office Action of October 16, 2006, includes a number of reasons some of the foregoing arguments were found unpersuasive by the examiner. These reasons are discussed herein. The examiner first stated:

> Contrary to Applicant's arguments Clark et al. as indicated above does disclose the use of an alkyl ester and alkyl alpha cyanoacrylate as it specifically incorporates by reference the US Patent, Kronenthal et al., and identifies the use of 2-octyl cyanoacrylate which is an alkyl alpha cyanoacrylate.

*Office Action mailed October 16, 2006, page 5.* As discussed above, Appellant disagrees.

Clark claims a composition which comprises at least two different monomers. Clark also discloses a number of cyanoacrylates as well as non-cyanoacrylate types of monomers such as vinylidene cyanides, dialkyl methylene malonates, acylacrylonitriles, vinyl sulfinates and vinyl sulfonates, among others. *Column 4, lines 1-7.* No guidance regarding which two

different monomers should be used is provided. In addition, Clark lacks any disclosure regarding particular monomer combinations useful for biodegradability or absorption rate of any polymerized compositions which might suggest a combination providing such characteristics. Despite the lack of disclosure in Clark of any specific combinations of cyanoacrylate monomers as claimed, the Examiner asserts that Clark does include such disclosure due to the incorporation by reference of Kronenthal and the identification in Clark of the use of 2-octyl cyanoacrylate. However, Kronenthal is cited in Clark for the procedure of making alkyl ester cyanoacrylates. *Clark, column 5, lines 42-43.* No disclosure regarding a specific combination of alkyl ester cyanoacrylates and alkyl α-cyanoacrylates is found either in Clark or in Kronenthal. Kronenthal describes carboalkoxyalkyl cyanoacrylates but not combinations of cyanoacrylate monomers of different species. Neither patent nor a combination thereof suggest the claimed monomers and initiator or accelerator as claimed. In view thereof, the comments of the examiner do not appear to provide any motivation for the combination of Clark or Kronenthal such that the resulting combination would provide the composition defined in the rejected claims.

In addition, Kronenthal describes alkyl 2-cyanoacrylates as having failed to have the required properties of low toxicity and adequate absorption by the tissues. The Kronenthal specification states that methyl 2-cyanoacrylate gives rise to a severe inflammatory response at the site of application and the n-butyl and isobutyl 2-cyanoacrylate monomers are not absorbed well (if at all) by the tissues. *Column 1, lines 14-33.* In view of this disclosure, one of ordinary skill in the art would not have been motivated to combine alkyl α-cyanoacrylates with other cyanoacrylate monomers since undesirable properties are attributed to the alkyl α-cyanoacrylates when used in a tissue application. Indeed, the examples distinguish the properties of the described carbalkoxyalkyl cyanoacrylates from alkyl 2-cyanoacrylates.

With regard to this issue, the Examiner stated:

> With respect to Kronenthal et al, it is immaterial what Kronenthal et al. does and does not disclose as the rejection herein is based on a combination of references. The applicant does not refute the fact that Kronenthal et al. discloses the use of alkyl ester acrylates and that they biodegrade faster than the alpha alkyl cyanoacrylate isobutyl 2-cyanoacrylate. Kronenthal must be read in view of Clark et al. which does discloses [sic] combinations of different cyanoacrylate monomers as well as the other references.

*Office Action mailed October 16, 2006, page 5.* These comments are in contradiction to the law as interpreted by the Court of Appeals for the Federal Circuit which has stated that a prior art reference must be considered in its entirety, i.e., as a whole, including portions that would lead away from the claimed invention. *W.L. Gore & Associates, Inc. v. Garlock, Inc.*, 721 F.2d 1540, 220 USPQ 303 (Fed. Cir. 1983), cert. denied, 469 U.S. 851 (1984). This is true even when the cited art is used in combination with other art. Kronenthal describes the use of alkyl α-cyanoacrylates in tissue adhesives as undesirable, thus, teaching away from using such types of cyanoacrylates. One of ordinary skill in the art would have considered this information along with the remainder of the disclosure of the cited art. *See, Eli Lilly, 471 F.3d at 1378* ("Though the '574 patent disclosed Compound '222, the patent expressed a preference for halogen containing compounds and specifically those with a halogenated substituent on the benzene ring in a location analogous to the chlorine in clozapine...The prior art references at the time of this invention taught away from using a non-halogenated compound as a substituent in the benzene ring....").

Hammerslag does not add to the combination set forth by the examiner because there is only a disclosure regarding polymerizable cyanoacrylates copolymerized with other compounds which affect the properties of the resulting material. Hammerslag does not disclose or *suggest* a combination of cyanoacrylate monomers or disclose or suggest a particular combination as claimed.

As to this issue, the Examiner stated:

> With respect to Hammerslag, a patent reference is prior art for all that it discloses. The fact the examples are related to other types of polymers does not teach away from the general disclosure that a given cyanoacrylate can be mixed with other substances to adjust biodegradation rates. There is nothing in Hammerslag that precludes another cyanoacrylate from being said substance. Again, since Clark et al. does disclose the combination of different cyanoacrylate monomers [it] is immaterial that Hammerslag does not explicitly disclose that the substance can be a cyanoacrylate monomer.

*Office Action mailed October 16, 2006, pages 5-6.* Appellant disagrees. First, that Hammerslag does not **preclude** something is not the standard under 35 U.S.C. § 103(a). For a combination of cited art, the fact finder must determine what the prior art actually teaches

(not what it may or may not preclude), whether it teaches away from the claimed invention, and whether it motivates a combination of teachings from different references. *Dystar*, 464 F.3d at 1360. The general disclosure of Hammerslag regarding combinations of monomers does not provide the requisite motivation to combine the particular types of monomers as claimed and the polymerization initiator or accelerator as claimed to provide advantages in absorbability as claimed.

As to the addition of EP '623 to the other cited art, EP '623 includes a claim which recites a monomer which is at least one member of a group of certain specific cyanoacrylate monomers. None of these monomers is an alkyl ester cyanoacrylate. Moreover, two of the listed members are referred to in Kronenthal as having poor properties with regard to biodegradation or histotoxicity. EP '623 does not disclose or suggest any combination of monomers with advantages in absorbability. Thus, adding the disclosure of EP '623 to the disclosure of the other patents would not have motivated one of ordinary skill in the art to combine the monomer species as claimed.

None of the cited art discloses or suggests the combination of a monomer species comprising an alkyl ester cyanoacrylate and a monomer species comprising an alkyl α-cyanoacrylate with an initiator or accelerator comprising a quaternary amine.

If the invention as defined in the rejected claims is considered as a whole, and the cited art documents are considered in their entirety, it is clear that the cited art, alone or in combination, does not disclose or suggest the biocompatible adhesive composition as claimed. In view thereof, a *prima facie* case has not been made with regard to any of independent claim 74 and dependent claims 76-86, 89-91, 95-98 and 100-102, and Appellant respectfully requests that this rejection be reversed.

**3. Claim 75**

Claim 75 is dependent on claim 74 and is directed to a biocompatible adhesive composition wherein the first monomer species and the second monomer species have different polymer absorption rates such that a polymer absorption rate of a faster absorbing monomer species is at least 10% faster than a polymer absorption rate of a slower absorbing monomer species. *Page 10, lines 22-24.*

Appellant relies on the description of the cited art given above. None of the cited art, alone or in combination, discloses or suggests a biocompatible adhesive composition comprising a first monomer species comprising an alkyl ester cyanoacrylate, a second monomer species different from the first monomer species comprising an alkyl α-cyanoacrylate and a polymerization initiator or accelerator comprising a quaternary amine. None of the cited art describes or suggests a first monomer species with a first polymer absorption rate and a second monomer species with a second polymer absorption rate different from the first polymer absorption rate. In addition, none of the art, alone or in combination, relates to the absorption rates of a combination of first monomer species and second monomer species as claimed in claim 75 wherein the polymer absorption rate of the faster absorbing monomer species is at least 10% faster than a polymer absorption rate of a slower absorbing monomer species.

As discussed, Clark mentions a composition which comprises at least two different monomers, but does not provide any description or suggestion regarding the absorption rates of particular combinations of monomers. Kronenthal describes biodegradation rates but does not disclose or suggest combinations of particular types of monomers wherein the polymer absorption rate is as claimed. Hammerslag and EP '623 do not add any disclosure regarding absorption relevant to the subject matter of claim 75. In view of the foregoing, a *prima facie* case has not been made and Appellant respectfully requests that this rejection as applied to claim 75 be reversed.

**4. Claims 87-88**

Claim 87 is dependent on claim 74 and is directed to a biocompatible adhesive composition wherein the composition comprises a monomer blend comprising from about 25 to about 40 parts by weight butyl lactoyl cyanoacrylate and from about 60 to about 75 parts by weight octyl cyanoacrylate, at least one anionic stabilizer and at least one radical stabilizer. Claim 88 is dependent on claim 87 and is directed to a biocompatible adhesive composition wherein the anionic stabilizer comprises about 25 to about 100 ppm of sulfuric acid and from about 1 to about 50 ppm sulfur dioxide, and the radical stabilizer comprises

from about 100 to about 2000 ppm hydroquinone, from about 10 to about 200 ppm p-methoxyphenol, and from about 100 to about 10,000 ppm butylated hydroxyanisole.

Appellant relies on the description of the cited art given above. None of the cited art, alone or in combination, discloses or suggests a biocompatible adhesive composition comprising a first monomer species comprising an alkyl ester cyanoacrylate, a second monomer species different from the first monomer species comprising an alkyl α-cyanoacrylate and a polymerization initiator or accelerator comprising a quaternary amine. None of the cited art describes or suggests a first monomer species with a first polymer absorption rate and a second monomer species with a second polymer absorption rate different from the first polymer absorption rate. In addition, none of the cited art, alone or in combination, discloses or suggests a composition which comprises a monomer blend comprising from about 25 to about 40 parts by weight butyl lactoyl cyanoacrylate and from about 60 to about 75 parts by weight octyl cyanoacrylate, at least one anionic stabilizer and at least one radical stabilizer

As discussed, Clark mentions a composition which comprises at least two different monomers, but does not provide any description or suggestion regarding the particular monomers to be used together. Kronenthal only describes comonomers of carbalkoxyalkyl cyanoacrylates. Hammerslag and EP '623 do not add any disclosure relevant to the subject matter of claims 87-88. In view of the foregoing, a *prima facie* case has not been made and Appellant respectfully requests that this rejection as applied to claims 87-88 be reversed.

**5. Claim 92**

Claim 92 is dependent on claim 74 and is directed to a biocompatible adhesive composition further comprising about 20 ppm sulfuric acid, 0 to 20 ppm sulfur dioxide, 0 to 2000 ppm hydroquinone, 0 to 180 p-methoxyphenol and 0 to 2000 ppm butylated hydroxyanisole.

Appellant relies on the description of the cited art given above. None of the cited art, alone or in combination, discloses or suggests a biocompatible adhesive composition comprising a first monomer species comprising an alkyl ester cyanoacrylate, a second monomer species different from the first monomer species comprising an alkyl α-

cyanoacrylate and a polymerization initiator or accelerator comprising a quaternary amine. None of the cited art describes or suggests a first monomer species with a first polymer absorption rate and a second monomer species with a second polymer absorption rate different from the first polymer absorption rate. In addition, none of the cited art discloses or suggests a composition which comprises the specific amounts of components recited in claim 92 in a biocompatible adhesive composition according to claim 74.

The art provides for the use of stabilizers but not in combination with the composition as claimed. In view of the foregoing, a *prima facie* case has not been made and Appellant respectfully requests that this rejection as applied to claim 92 be reversed.

**6. Claim 93**

Claim 93 is dependent on claim 92 and is directed to the biocompatible adhesive composition of claim 92, wherein the first monomer species comprises butyl lactoyl cyanoacrylate and the second monomer species comprises octyl α-cyanoacrylate.

Appellant relies on the description of the cited art given above. None of the cited art, alone or in combination, discloses or suggests a biocompatible adhesive composition comprising a first monomer species comprising an alkyl ester cyanoacrylate, a second monomer species different from the first monomer species comprising an alkyl α-cyanoacrylate and a polymerization initiator or accelerator comprising a quaternary amine. None of the cited art describes or suggests a first monomer species with a first polymer absorption rate and a second monomer species with a second polymer absorption rate different from the first polymer absorption rate. In addition, none of the cited art discloses or suggests a composition which comprises the specific monomer species claimed.

As discussed, Clark mentions a composition which comprises at least two different monomers, but does not provide any description or suggestion regarding the particular monomers to be used together. Kronenthal describes comonomers of alkyl ester cyanoacrylates. Hammerslag and EP '623 do not add any disclosure relevant to the subject matter of claim 93. In view of the foregoing, a *prima facie* case has not been made and Appellant respectfully requests that this rejection as applied to claim 93 be reversed.

**7. Claim 99**

Claim 99 is dependent on claim 74 and is directed to a biocompatible adhesive composition wherein the polymerization initiator or accelerator polymerizes a mixture of the first monomer species and the second monomer species in less than 3 minutes.

Appellant relies on the description of the cited art given above. None of the cited art, alone or in combination, discloses or suggests a biocompatible adhesive composition comprising a first monomer species comprising an alkyl ester cyanoacrylate, a second monomer species different from the first monomer species comprising an alkyl α-cyanoacrylate and a polymerization initiator or accelerator comprising a quaternary amine. None of the cited art, alone or in combination, describes or suggests a first monomer species with a first polymer absorption rate and a second monomer species with a second polymer absorption rate different from the first polymer absorption rate. In addition, none of the cited art includes any description or suggestion regarding the time of polymerization for the monomer species as claimed in combination.

As discussed, Clark mentions a composition which comprises at least two different monomers, but does not provide any description or suggestion regarding the particular monomers to be used together or the ability of a polymerization initiator or accelerator to provide the claimed polymerization time. Kronenthal describes comonomers of alkyl ester cyanoacrylates but does not disclose use of specific polymerization initiators or accelerators. Hammerslag does not disclose use of polymerization initiators or accelerators. EP '623 does not provide any description or suggestion regarding the particular monomers to be used together or the ability of a polymerization initiator or accelerator to provide the claimed polymerization time. In view of the foregoing, a *prima facie* case has not been made and Appellant respectfully requests that this rejection as applied to claim 99 be reversed.

**C. Claims 74-93 and 95-102 are patentable under 35 U.S.C. § 103(a) over Clark et al., U.S. Patent No. 5,981,621, in view of Kronenthal et al., U.S. Patent No. 3,995,641, Hammerslag, U.S. Patent No. 6,386,203, and EP 0 965 623, in further view of Banitt et al., U.S. Patent No. 3,559,652, and Collins et al.**

**1. The Cited Art**

Clark, Kronenthal, Hammerslag and EP '623 are discussed above.

Banitt et al., U.S. Patent No. 3,559,652 (hereinafter "Banitt") is directed to a method for surgically adhering living tissues and effecting hemostasis therein by means of a rapidly polymerizing composition which comprises alkoxyalkyl 2-cyanoacrylates. *Abstract.* The alkoxyalkyl 2-cyanoacrylates of Banitt are described as providing the desired absorbability, in contrast to alkyl cyanoacrylates.

Collins describes cure rates of cyanoacrylate tissue adhesives. In particular, Collins compares rates of polymerization for the series of N-alkyl-2-cyanoacrylates, methyl through octyl.

**2. Claims 74, 76-86, 89-91, 95-98 and 100-102**

Banitt discloses a combination of alkoxyalkyl 2-cyanoacrylates and alkyl cyanoacrylates (*column 4, lines 1-7*). Banitt states:

> The utility of alkoxy alkyl 2-cyanoacrylates in the adhesives of the invention results from the unusual combination of advantageous properties which makes them particularly adaptable for use in biological systems, for example, the rate of polymerization of the alkoxyalkyl 2-cyanoacrylates of the invention is such that it allows rapid and secure bonding, but yet allows the surgeon adequate working time before the bond becomes firmly fixed.

*Column 2, lines 22-29 (emphasis added).*

Additionally, Banitt does not describe or suggest the use of monomers with differing absorption rates with a polymerization initiator or accelerator comprising a quaternary amine to provide a polymer absorption rate as desired. Since Banitt is directed to the use of ether cyanoacrylates, which were found to have particular advantageous properties, Banitt does not add anything to the combination of cited art already presented. One of ordinary skill in the art would not have modified the teachings of Banitt to apply to alkyl ester cyanoacrylates in view of the very specific language of Banitt referring to the advantages of ether cyanoacrylates.

Collins does not describe combinations of cyanoacrylate monomers and only describes tests on alkyl 2-cyanoacrylates, not other types of cyanoacrylate monomers. Collins describes the findings made with regard to alkyl cyanoacrylates as follows:

> The n-alkyl-2-cyanoacrylates, from methyl to octyl, exhibit a reverse order of rate of effective polymerization in biological systems as compared to water. In contrast to aqueous systems, also, the shorter chain members do not spread on biological fluids, whereas the higher homologues spread rapidly both on water and on biological fluids.
>
> Because of these phenomena, the longer chain N-alkyl-cyanoacrylates should prove more effective tissue adhesive and hemostasis inducing compounds than the lower homologues, particularly the methyl monomer. One factor remaining in favor of the methyl monomer is its rapid biodegradation. An adhesive combining the low acute toxicity and spreading and rapidly polymerizing characteristics of the higher homologues with the biodegradability of the methyl monomer would be highly desirable.

*Collins, page 432.*

The Examiner apparently relies on this discussion in Collins for motivation to combine cyanoacrylate monomers with different biodegradation rates. *Office Action mailed October 16, 2006, pages 9-11.* However, Collins states that an adhesive combining the low acute toxicity and spreading and rapidly polymerizing characteristics of the higher homologues with the biodegradability of the methyl monomer would be highly desirable. Collins does not provide any direction as to how such an adhesive combining the described characteristics might be obtained. At most, any motivation provided in Collins to combine cyanoacrylate monomers only concerns the combination of different homologues of the alkyl cyanoacrylates. No other species of cyanoacrylates is discussed or suggested. Thus, Collins does not suggest providing the combination of monomers as claimed of alkyl ester cyanoacrylates with alkyl α-cyanoacrylates since there is no suggestion that such cyanoacrylates have differing absorption rates nor that a combination thereof would be advantageous and/or would provide a third polymer absorption rate different from the polymer absorption rates of the polymers formed from the different monomer species as claimed. Moreover, Collins does not add any suggestion regarding polymerization rates or an initiator or accelerator needed to control the polymerization rate.

None of the cited art, alone or in combination, discloses or suggests the combination of a monomer species with a first polymer absorption rate comprising an alkyl ester cyanoacrylate and a monomer species with a second polymer absorption rate different from the first polymer absorption rate comprising an alkyl α-cyanoacrylate with an initiator or

accelerator comprising a quaternary amine.

If the invention as defined in the rejected claims is considered as a whole, and the cited art documents are considered in their entirety, it is clear that the cited art, alone or in combination, does not disclose or suggest the biocompatible adhesive composition as claimed. In view thereof, a *prima facie* case has not been made with regard to any of independent claim 74 and dependent claims 76-86, 89-91, 95-98 and 100-102, and Appellant respectfully requests that this rejection be reversed.

**3. Claim 75**

Claim 75 is dependent on claim 74 and is directed to a biocompatible adhesive composition wherein the first monomer species and the second monomer species have different polymer absorption rates such that a polymer absorption rate of a faster absorbing monomer species is at least 10% faster than a polymer absorption rate of a slower absorbing monomer species. *Page 10, lines 22-24.*

Appellant relies on the description of the cited art given above. None of the cited art, alone or in combination, discloses or suggests a biocompatible adhesive composition comprising a first monomer species comprising an alkyl ester cyanoacrylate, a second monomer species different from the first monomer species comprising an alkyl α-cyanoacrylate and a polymerization initiator or accelerator comprising a quaternary amine. None of the cited art, alone or in combination, describes or suggests a first monomer species with a first polymer absorption rate and a second monomer species with a second polymer absorption rate different from the first polymer absorption rate. In addition, none of the art relates the absorption rates of a combination of first monomer species and second monomer species as claimed in claim 75 wherein the polymer absorption rate of the faster absorbing monomer species is at least 10% faster than a polymer absorption rate of a slower absorbing monomer species.

As discussed, Clark mentions a composition which comprises at least two different monomers, but does not provide any description or suggestion regarding the absorption rates of particular combinations of monomers. Kronenthal describes biodegradation rates but does not disclose or suggest combinations of particular types of monomers wherein the polymer

absorption rate is as claimed. Hammerslag and EP '623 do not add any disclosure regarding absorption relevant to the subject matter of claim 75. Banitt is directed to ether cyanoacrylates. Collins describes alkyl cyanoacrylates. In view of the foregoing, a *prima facie* case has not been made and Appellant respectfully requests that this rejection as applied to claim 75 be reversed.

**4. Claims 87-88**

Claim 87 is dependent on claim 74 and is directed to a biocompatible adhesive composition wherein the composition comprises a monomer blend comprising from about 25 to about 40 parts by weight butyl lactoyl cyanoacrylate and from about 60 to about 75 parts by weight octyl cyanoacrylate, at least one anionic stabilizer and at least one radical stabilizer. Claim 88 is dependent on claim 87 and is directed to a biocompatible adhesive composition wherein the anionic stabilizer comprises about 25 to about 100 ppm of sulfuric acid and from about 1 to about 50 ppm sulfur dioxide, and the radical stabilizer comprising from about 100 to about 2000 ppm hydroquinone, from about 10 to about 200 ppm p-methoxyphenol, and from about 100 to about 10,000 ppm butylated hydroxyanisole.

Appellant relies on the description of the cited art given above. None of the cited art, alone or in combination, discloses or suggests a biocompatible adhesive composition comprising a first monomer species comprising an alkyl ester cyanoacrylate, a second monomer species different from the first monomer species comprising an alkyl α-cyanoacrylate and a polymerization initiator or accelerator comprising a quaternary amine. None of the cited art, alone or in combination, describes or suggests a first monomer species with a first polymer absorption rate and a second monomer species with a second polymer absorption rate different from the first polymer absorption rate. In addition, none of the cited art discloses or suggests a composition which comprises a monomer blend comprising from about 25 to about 40 parts by weight butyl lactoyl cyanoacrylate and from about 60 to about 75 parts by weight octyl cyanoacrylate, at least one anionic stabilizer and at least one radical stabilizer

As discussed, Clark mentions a composition which comprises at least two different monomers, but does not provide any description or suggestion regarding the particular

monomers to be used together. Kronenthal describes comonomers of alkyl ester cyanoacrylates. Hammerslag and EP '623 do not add any disclosure relevant to the subject matter of claims 87-88. Banitt is directed to ether cyanoacrylates. Collins describes alkyl cyanoacrylates. In view of the foregoing, a *prima facie* case has not been made and Appellant respectfully requests that this rejection as applied to claims 87-88 be reversed.

**5. Claim 92**

Claim 92 is dependent on claim 74 and is directed to a biocompatible adhesive composition further comprising about 20 ppm sulfuric acid, 0 to 20 ppm sulfur dioxide, 0 to 2000 ppm hydroquinone, 0 to 180 p-methoxyphenol and 0 to 2000 ppm butylated hydroxyanisole.

Appellant relies on the description of the cited art given above. None of the cited art, alone or in combination, discloses or suggests a biocompatible adhesive composition comprising a first monomer species comprising an alkyl ester cyanoacrylate, a second monomer species different from the first monomer species comprising an alkyl α-cyanoacrylate and a polymerization initiator or accelerator comprising a quaternary amine. None of the cited art, alone or in combination, describes or suggests a first monomer species with a first polymer absorption rate and a second monomer species with a second polymer absorption rate different from the first polymer absorption rate. In addition, none of the cited art discloses or suggests a composition which comprises the specific amounts of components recited in claim 92 in a biocompatible adhesive composition according to claim 74.

The art cited provides for the use of stabilizers but not in combination with the monomers as claimed. In view of the foregoing, a *prima facie* case has not been made and Appellant respectfully requests that this rejection as applied to claim 92 be reversed.

**6. Claim 93**

Claim 93 is dependent on claim 92 and is directed to the biocompatible adhesive composition of claim 92, wherein the first monomer species comprises butyl lactoyl cyanoacrylate and the second monomer species comprises octyl α-cyanoacrylate.

Appellant relies on the description of the cited art given above. None of the cited art, alone or in combination, discloses or suggests a biocompatible adhesive composition comprising a first monomer species comprising an alkyl ester cyanoacrylate, a second monomer species different from the first monomer species comprising an alkyl α-cyanoacrylate and a polymerization initiator or accelerator comprising a quaternary amine. None of the cited art, alone or in combination, describes or suggests a first monomer species with a first polymer absorption rate and a second monomer species with a second polymer absorption rate different from the first polymer absorption rate. In addition, none of the cited art discloses or suggests a composition which comprises the specific monomer species claimed.

As discussed, Clark mentions a composition which comprises at least two different monomers, but does not provide any description or suggestion regarding the particular monomers to be used together. Kronenthal describes combinations of alkyl ester cyanoacrylates. Hammerslag and EP '623 do not add any disclosure relevant to the subject matter of claim 93. Banitt is directed to ether cyanoacrylates. Collins describes alkyl cyanoacrylates. In view of the foregoing, a *prima facie* case has not been made and Appellant respectfully requests that this rejection as applied to claim 93 be reversed.

**7. Claim 99**

Claim 99 is dependent on claim 74 and is directed to a biocompatible adhesive composition wherein the polymerization initiator or accelerator polymerizes a mixture of the first monomer species and the second monomer species in less than 3 minutes.

Appellant relies on the description of the cited art given above. None of the cited art discloses or suggests a biocompatible adhesive composition comprising a first monomer species comprising an alkyl ester cyanoacrylate, a second monomer species different from the first monomer species comprising an alkyl α-cyanoacrylate and a polymerization initiator or accelerator comprising a quaternary amine. None of the cited art describes or suggests a first monomer species with a first polymer absorption rate and a second monomer species with a second polymer absorption rate different from the first polymer absorption rate. In

addition, none of the cited art includes any description or suggestion regarding the time of polymerization for the monomer species as claimed in combination.

As discussed, Clark mentions a composition which comprises at least two different monomers, but does not provide any description or suggestion regarding the particular monomers to be used together or the ability of a polymerization initiator or accelerator to provide the claimed polymerization time. Kronenthal only describes combinations of alkyl ester cyanoacrylates but does not disclose use of polymerization initiators or accelerators. Hammerslag does not disclose use of specific polymerization initiators or accelerators or rates of polymerization. EP '623 does not provide any description or suggestion regarding the particular monomers to be used together or the ability of a polymerization initiator or accelerator to provide the claimed polymerization time. Banitt and Collins do not specify the monomers as claimed or the polymerization rates as claimed. In view of the foregoing, a *prima facie* case has not been made and Appellant respectfully requests that this rejection as applied to claim 99 be reversed.

**D. Claims 74-93 and 95-102 are patentable under 35 U.S.C. § 103(a) over Berger et al., U.S. Patent No. 5,998,472, in view of Kronenthal et al., U.S. Patent No. 3,995,641, Hammerslag, U.S. Patent No. 6,386,203, and Clark et al., U.S. Patent No. 5,981,621.**

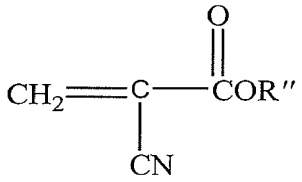
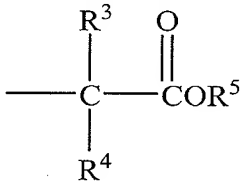
**1. The Cited Art**

U.S. Patent No. 5,998,472, issued to Berger et al. (hereinafter "Berger") is directed to mixed cyanoacrylate ester compositions specifically formulated for topical application onto intact or broken human skin. Berger discloses that the addition of a $C_{10}$-$C_{12}$ alkyl cyanoacrylate ester to a $C_1$ to $C_8$ alkyl cyanoacrylate ester provides for a composition which forms a flexible cyanoacrylate polymer on mammalian skin without the need to add a plasticizer. *Column 2, lines 62-67.* The polymerizable alkyl cyanoacrylate ester compositions described rapidly polymerize in the presence of water vapor or tissue protein, and these prepolymers bond human skin tissue without causing histotoxicity or cytotoxicity.

The compositions can be used to form a polymer layer on mammalian skin which layer inhibits blister formation, which inhibits irritation arising from prosthetic devices, which inhibits skin irritation and infection due to incontinence, which can be used as a

surgical drape, and the like. *Column 9, lines 26-30.*

Berger also states as follows:

> It is contemplated that the flexibility of polymeric films formed on mammalian skin from cyanoacrylate esters can be improved by the addition of a effective amount of a $C_{10}$ to $C_{12}$ cyanoacrylate ester wherein such cyanoacrylate esters are represented by the formula
>
> 
>
> wherein R" is alkenyl of 2 to 10 carbon atoms, cycloalkyl groups of from 5 to 8 carbon atoms, phenyl, 2-ethoxyethyl, 3-methoxybutyl, or a substituent of the formula:
>
> 
>
> wherein $R^3$ and $R^4$ are independently selected from the group consisting of hydrogen and methyl, and $R^5$ is selected from the group consisting of alkyl of from 1 to 6 carbon atoms, alkenyl of from 2 to 6 carbon atoms, alkynyl of from 2 to 6 carbon atoms, cycloalkyl of from 3 to 8 carbon atoms, aralkyl selected from the group consisting of benzyl, methylbenzyl and phenylethyl, phenyl, and phenyl substituted with 1 to 3 substituents selected from the group consisting of hydroxy, chloro, bromo, nitro, alkyl of 1 to 4 carbon atoms, and alkoxy of from 1 to 4 carbon atoms.

*Column 10, line 53-column 11, line 18.*

The other cited art is described above.

**2. Claims 74, 76-86, 89-91, 95-98 and 100-102**

Claim 74 is directed to a biocompatible adhesive composition and requires a first monomer species comprising an alkyl ester cyanoacrylate, a second monomer species different from the first monomer species comprising an alkyl α-cyanoacrylate, and a polymerization initiator or accelerator comprising a quaternary amine. The first monomer species has a first polymer absorption rate and the second monomer species has a second

polymer absorption rate different from the first polymer absorption rate. The biocompatible adhesive composition has a third polymer absorption rate different from the first and second polymer absorption rates.

The scope and content of the art have been discussed. The examiner acknowledges that a difference between the cited art and the claimed invention is that the prior art does not expressly disclose combination of alkyl ester cyanoacrylate and other monomer based on difference in biodegradation rate. The examiner then broadly asserts that the "prior art amply suggests the same" and further "it would have been well within the skill of and one of ordinary skill in the art would have been motivated to combine" different monomers with various expectations. However, to establish a *prima facie* case of obviousness based on a combination of elements in the prior art, the law requires a motivation to select the references and to combine them in the particular claimed manner to reach the claimed invention. *Eli Lilly and Co.*, 471 F.3d at 1379. The requisite motivation is lacking for the selection of the art as cited and the combination thereof to reach the claimed invention.

The examiner states that one of skill in the art would have been motivated to combine an alkyl ester cyanoacrylate with a different cyanoacrylate with the expectation that biodegradation of the composition could be adjusted readily by modifying the ratio of the monomers. However, while Berger describes a combination of monomers, Berger does not contain any disclosure regarding the biodegradation of the composition obtained. Rather, Berger is concerned with the flexibility of the material and the ability to prepare a flexible material without a plasticizer. Moreover, the compositions of Berger are intended for topical use; thus, there is no teaching or suggestion regarding biodegradation made for the uses taught for the compositions described in Berger and no conclusions regarding biodegradation would be made by one of skill in the art regarding those compositions.

The other cited art also lacks the motivation asserted. Kronenthal describes the advantageous biodegradation properties of alkyl ester cyanoacrylates, but does not include any description of modifying the ratio of combination of monomers to change the biodegradation rates. Rather, Kronenthal illustrates the disadvantages of using alkyl 2-cyanoacrylates due to problems with degradation for higher homologues and histotoxicity for lower homologues. Hammerslag includes disclosure regarding biodegradation of

cyanoacrylate monomers, but not in combination. Clark lacks any disclosure regarding biodegradation of particular monomers or particular combinations of cyanoacrylate monomers. Thus, the expectation referred to by the examiner is completely lacking from the cited art, even in combination.

The examiner then concludes by stating that one of ordinary skill in the art would have been motivated to use benzalkonium chloride with the expectation that is would act as a polymerization initiator. Berger describes polymerization in the presence of water vapor or tissue protein. Kronenthal describes polymerization in the presence of moisture. Hammerslag mentions initiators, cross-linkers, catalysts, and other compounds which aid an adhesive or closure medium in setting up, but does not list any particular compounds for such use. Clark describes initiators and includes a long list of possible initiators. *Column 11, lines 18-67.* None of the cited art, even in combination, provides motivation to use the initiator or accelerator as claimed.

As shown, the examiner's rejection merely selects bits and pieces of a number of patents without any showing that one of ordinary skill in the art would have combined the various features to obtain the biocompatible adhesive composition as claimed. Rather, as described in the specification, the selection of monomer will affect the absorption rate of the resultant polymer as well as the polymerization rate of the monomer. The combination of monomers as claimed and the polymerization initiator or accelerator as claimed provides an adhesive composition which has advantageous absorbability properties as claimed. None of the art cited recognizes the problem of polymerization rate when different monomer species are combined or how the monomers should be managed to obtain a desired absorption rate. The law requires a motivation to select the references and to combine them in the particular claimed manner to reach the claimed invention. *Eli Lilly*, 471 F.3d at 1379. Such motivation is not found in the rejection over Berger, Kronenthal, Hammerslag and Clark. In view thereof, a *prima facie* case has not been made with regard to any of independent claim 74 and dependent claims 76-86, 89-91, 95-98 and 100-102, and Appellant respectfully requests that this rejection be reversed.

**3. Claim 75**

Claim 75 is dependent on claim 74 and is directed to a biocompatible adhesive composition wherein the first monomer species and the second monomer species have different polymer absorption rates such that a polymer absorption rate of a faster absorbing monomer species is at least 10% faster than a polymer absorption rate of a slower absorbing monomer species. *Page 10, lines 22-24.*

Appellant relies on the description of the cited art given above. None of the cited art, alone or in combination, discloses or suggests a biocompatible adhesive composition comprising a first monomer species comprising an alkyl ester cyanoacrylate, a second monomer species different from the first monomer species comprising an alkyl α-cyanoacrylate and a polymerization initiator or accelerator comprising a quaternary amine. None of the cited art, alone or in combination, describes or suggests a first monomer species with a first polymer absorption rate and a second monomer species with a second polymer absorption rate different from the first polymer absorption rate. In addition, none of the art relates the absorption rates of a combination of first monomer species and second monomer species as claimed in claim 75 wherein the polymer absorption rate of the faster absorbing monomer species is at least 10% faster than a polymer absorption rate of a slower absorbing monomer species.

As discussed, Berger mentions a composition which comprises at least two different monomers, but does not provide any description or suggestion regarding the absorption rates of particular combinations of monomers. Kronenthal describes biodegradation rates but does not disclose or suggest combinations of particular types of monomers or describe combinations for monomers wherein the polymer absorption rate is as claimed. Hammerslag and Clark do not add any disclosure regarding absorption rates relevant to the subject matter of claim 75. In view of the foregoing, a prima facie case has not been made and Appellant respectfully requests that this rejection as applied to claim 75 be reversed.

**4. Claims 87-88**

Claim 87 is dependent on claim 74 and is directed to a biocompatible adhesive composition wherein the composition comprises a monomer blend comprising from about 25

to about 40 parts by weight butyl lactoyl cyanoacrylate and from about 60 to about 75 parts by weight octyl cyanoacrylate, at least one anionic stabilizer and at least one radical stabilizer. Claim 88 is dependent on claim 87 and is directed to a biocompatible adhesive composition wherein the anionic stabilizer comprises about 25 to about 100 ppm of sulfuric acid and from about 1 to about 50 ppm sulfur dioxide, and the radical stabilizer comprising from about 100 to about 2000 ppm hydroquinone, from about 10 to about 200 ppm p-methoxyphenol, and from about 100 to about 10,000 ppm butylated hydroxyanisole.

Appellant relies on the description of the cited art given above. None of the cited art, alone or in combination, discloses or suggests a biocompatible adhesive composition comprising a first monomer species comprising an alkyl ester cyanoacrylate, a second monomer species different from the first monomer species comprising an alkyl α-cyanoacrylate and a polymerization initiator or accelerator comprising a quaternary amine. None of the cited art, alone or in combination, describes or suggests a first monomer species with a first polymer absorption rate and a second monomer species with a second polymer absorption rate different from the first polymer absorption rate. In addition, none of the cited art discloses or suggests a composition which comprises a monomer blend comprising from about 25 to about 40 parts by weight butyl lactoyl cyanoacrylate and from about 60 to about 75 parts by weight octyl cyanoacrylate, at least one anionic stabilizer and at least one radical stabilizer

As discussed, Berger mentions a composition which comprises at least two different monomers, but does not provide any description or suggestion regarding the specific monomers claimed. Kronenthal lacks any disclosure or suggestion of a combination of monomers as claimed. Hammerslag and Clark do not add any disclosure regarding particular monomer compositions relevant to the subject matter of claims 87-88. In view of the foregoing, a *prima facie* case has not been made and Appellant respectfully requests that this rejection as applied to claims 87-88 be reversed.

**5. Claim 92**

Claim 92 is dependent on claim 74 and is directed to a biocompatible adhesive composition further comprising about 20 ppm sulfuric acid, 0 to 20 ppm sulfur dioxide, 0 to

2000 ppm hydroquinone, 0 to 180 p-methoxyphenol and 0 to 2000 ppm butylated hydroxyanisole.

Appellant relies on the description of the cited art given above. None of the cited art, alone or in combination, discloses or suggests a biocompatible adhesive composition comprising a first monomer species comprising an alkyl ester cyanoacrylate, a second monomer species different from the first monomer species comprising an alkyl α-cyanoacrylate and a polymerization initiator or accelerator comprising a quaternary amine. None of the cited art, alone or in combination, describes or suggests a first monomer species with a first polymer absorption rate and a second monomer species with a second polymer absorption rate different from the first polymer absorption rate. In addition, none of the cited art discloses or suggests a composition which comprises the specific amounts of components recited in claim 92 in a biocompatible adhesive composition according to claim 74.

The art provides for the use of stabilizers but not in combination with the monomers and an initiator or accelerator as claimed. In view of the foregoing, a *prima facie* case has not been made and Appellant respectfully requests that this rejection as applied to claim 92 be reversed.

**6. Claim 93**

Claim 93 is dependent on claim 92 and is directed to the biocompatible adhesive composition of claim 92, wherein the first monomer species comprises butyl lactoyl cyanoacrylate and the second monomer species comprises octyl α-cyanoacrylate.

Appellant relies on the description of the cited art given above. None of the cited art, alone or in combination, discloses or suggests a biocompatible adhesive composition comprising a first monomer species comprising an alkyl ester cyanoacrylate, a second monomer species different from the first monomer species comprising an alkyl α-cyanoacrylate and a polymerization initiator or accelerator comprising a quaternary amine. None of the cited art, alone or in combination, describes or suggests a first monomer species with a first polymer absorption rate and a second monomer species with a second polymer absorption rate different from the first polymer absorption rate. In addition, none of the cited

art discloses or suggests a composition which comprises the specific monomer species claimed.

As discussed, Berger mentions a composition which comprises at least two different monomers, but does not provide any description or suggestion regarding the specifically claimed monomer species. Kronenthal does not disclose or suggest combinations of particular types of monomers as claimed. Hammerslag and Clark do not add any disclosure relevant to the subject matter of claim 93. In view of the foregoing, a *prima facie* case has not been made and Appellant respectfully requests that this rejection as applied to claim 93 be reversed.

**7. Claim 99**

Claim 99 is dependent on claim 74 and is directed to a biocompatible adhesive composition wherein the polymerization initiator or accelerator polymerizes a mixture of the first monomer species and the second monomer species in less than 3 minutes.

Appellant relies on the description of the cited art given above. None of the cited art, alone or in combination, discloses or suggests a biocompatible adhesive composition comprising a first monomer species comprising an alkyl ester cyanoacrylate, a second monomer species different from the first monomer species comprising an alkyl α-cyanoacrylate and a polymerization initiator or accelerator comprising a quaternary amine. None of the cited art, alone or in combination, describes or suggests a first monomer species with a first polymer absorption rate and a second monomer species with a second polymer absorption rate different from the first polymer absorption rate. In addition, none of the cited art includes any description or suggestion regarding the time of polymerization for the monomer species as claimed in combination.

As discussed, Berger mentions a composition which comprises at least two different monomers, but does not provide any description or suggestion regarding polymerization rates of such monomers. Kronenthal describes biodegradation rates but does not disclose or suggest polymerization rates for particular types of monomers. Hammerslag and Clark do not add any disclosure regarding polymerization rates relevant to the subject matter of claim

99. In view of the foregoing, a *prima facie* case has not been made and Appellant respectfully requests that this rejection as applied to claim 99 be reversed.

For the reasons set forth above, Appellant respectfully submits that claims 74-93 and 95-102 are allowable over the cited art. Appellant respectfully requests that the final rejection of claims 74-93 and 95-102 be reversed.

**Note: For convenience of detachment without disturbing the integrity of the remainder of pages of this Appeal Brief, Appellant's APPENDICES VIII-X are attached following the signatory portion of this Appeal Brief.**

The Commissioner is hereby authorized to charge any additional fees, or credit any overpayment, associated with the filing of this paper to Deposit Account No. 50-3218.

Respectfully submitted,

Date: JUNE 16, 2008 By: _____

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## VIII. CLAIMS APPENDIX

CLAIMS ON APPEAL

Claim 74 A biocompatible adhesive composition comprising:

a first monomer species comprising an alkyl ester cyanoacrylate,

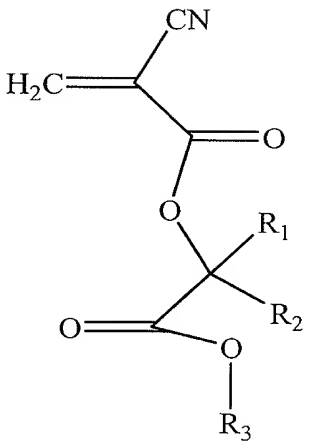
a second monomer species different from the first monomer species comprising an alkyl α-cyanoacrylate, and

a polymerization initiator or accelerator comprising a quaternary amine,

wherein the first monomer species has a first polymer absorption rate and the second monomer species has a second polymer absorption rate different from the first polymer absorption rate and the biocompatible adhesive composition has a third polymer absorption rate different from the first and second polymer absorption rates.

Claim 75 The biocompatible adhesive composition of claim 74, wherein the first monomer species and the second monomer species have different polymer absorption rates such that a polymer absorption rate of a faster absorbing monomer species is at least 10% faster than a polymer absorption rate of a slower absorbing monomer species.

Claim 76 The biocompatible adhesive composition of claim 74, wherein said alkyl ester cyanoacrylate has the formula




wherein $R_1$ and $R_2$ are independently H, a straight, branched or cyclic alkyl group, or are combined together in a cyclic alkyl group, and $R_3$ is a straight, branched or cyclic alkyl group.

Claim 77 The biocompatible adhesive composition of claim 76, wherein $R_1$ and $R_2$ are independently H or a $C_1$, $C_2$ or $C_3$ alkyl group and $R_3$ is a $C_1$-$C_{16}$ alkyl group.

Claim 78 The biocompatible adhesive composition of claim 74, wherein said alkyl ester cyanoacrylate is selected from the group consisting of butyl lactoyl cyanoacrylate, butyl glycoloyl cyanoacrylate, isopropyl glycoloyl cyanoacrylate, ethyl lactoyl cyanoacrylate, and ethyl glycoloyl cyanoacrylate.

Claim 79 The biocompatible adhesive composition of claim 74, wherein said second monomer species is an alkyl α-cyanoacrylate having an alkyl group of from about 2 to about 12 carbon atoms.

Claim 80 The biocompatible adhesive composition of claim 79, wherein said second monomer species is selected from the group consisting of octyl α-cyanoacrylate, hexyl α-cyanoacrylate, butyl α-cyanoacrylate and ethyl α-cyanoacrylate.

Claim 81 The biocompatible adhesive composition of claim 74, wherein a weight ratio of said first monomer species to said second monomer species is from about 1:99 to about 99:1.

Claim 82 The biocompatible adhesive composition of claim 74, wherein a weight ratio of said first monomer species to said second monomer species is from about 10:90 to about 90:10.

Claim 83 The biocompatible adhesive composition of claim 74, wherein a weight ratio of said first monomer species to said second monomer species is from about 15:85 to about 85:15.

Claim 84 The biocompatible adhesive composition of claim 74, wherein a weight ratio of said first monomer species to said second monomer species is from about 25:75 to about 75:25.

Claim 85 The biocompatible adhesive composition of claim 74, wherein said first monomer species comprises butyl lactoyl cyanoacrylate and said second monomer species comprises octyl α-cyanoacrylate.

Claim 86 The biocompatible adhesive composition of claim 74, wherein said composition further comprises at least one additive selected from the group consisting of anionic stabilizing agents, free radical stabilizing agents, colorants, and plasticizers.

Claim 87 The biocompatible adhesive composition of claim 74, wherein said composition comprises:

a monomer blend comprising from about 25 to about 40 parts by weight butyl lactoyl cyanoacrylate and from about 60 to about 75 parts by weight octyl cyanoacrylate (OCA);

at least one anionic stabilizer; and

at least one radical stabilizer.

Claim 88 The biocompatible adhesive composition of claim 87, wherein said at least one anionic stabilizer comprises about 25 to about 100 ppm of sulfuric acid and from about 1 to about 50 ppm sulfur dioxide, and said at least one radical stabilizer comprises from about 100 to about 2000 ppm hydroquinone, from about 10 to about 200 ppm p-methoxyphenol, and from about 100 to about 10,000 ppm butylated hydroxyanisole.

Claim 89 The biocompatible adhesive composition of claim 86, wherein said composition further comprises at least one additive selected from the group consisting of anionic stabilizing agents, free radical stabilizing agents and plasticizers, and the additive is present in an amount of up to 25 weight % based on a total weight of the composition.

Claim 90 The biocompatible adhesive composition of claim 86, wherein said composition further comprises at least one additive selected from the group consisting of anionic stabilizing agents, free radical stabilizing agents and plasticizers, and the additive is present in an amount of up to 10 weight % based on a total weight of the composition.

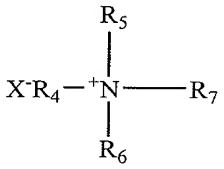
Claim 91 The biocompatible adhesive composition of claim 86, wherein said composition further comprises at least one additive selected from the group consisting of anionic stabilizing agents, free radical stabilizing agents and plasticizers, and the additive is present in an amount of up to 5 weight % based on a total weight of the composition.

Claim 92 The biocompatible adhesive composition of claim 74, wherein said composition further comprises about 20 ppm sulfuric acid, 0 to 20 ppm sulfur dioxide, 0 to 2000 ppm hydroquinone, 0 to 180 ppm p-methoxyphenol and 0 to 2000 ppm butylated hydroxyanisole.

Claim 93 The biocompatible adhesive composition of claim 92, wherein said first monomer species comprises butyl lactoyl cyanoacrylate and said second monomer species comprises octyl α-cyanoacrylate.

Claim 95 The biocompatible adhesive composition of claim 74, further comprising a second different polymerization initiator or accelerator.

Claim 96 The biocompatible adhesive composition of claim 74, wherein the quaternary amine has the formula



wherein $R_4$, $R_5$, $R_6$ and $R_7$ are each independently H or a substituted or unsubstituted straight, branched or cyclic alkyl group; a substituted or unsubstituted aromatic ring; a substituted or unsubstituted aralkyl group; or a substituted or unsubstituted alkyl or aromatic group including one or more hetero atoms; and $X^-$ is an anion.

Claim 97 The biocompatible adhesive composition of claim 74, wherein the quaternary amine is selected from the group consisting of domiphen bromide, butyrylcholine chloride, benzalkonium bromide and acetyl choline chloride.

Claim 98 The biocompatible adhesive composition of claim 74, wherein the quaternary amine is a benzalkonium halide having a chain length from about 12 to about 18 carbon atoms.

Claim 99 The biocompatible adhesive composition of claim 74, wherein the polymerization initiator or accelerator polymerizes a mixture of the first monomer species and the second monomer species in less than 3 minutes.

Claim 100 The biocompatible adhesive composition of claim 74, wherein the first monomer species and the second monomer species are present in an amount of at least 65 percent by weight of the biocompatible adhesive composition.

Claim 101 The biocompatible adhesive composition of claim 74, wherein at least the first monomer species forms a polymer that is absorbable.

Claim 102 A polymerized film formed by curing the biocompatible adhesive composition of claim 74.

## IX. EVIDENCE APPENDIX

EVIDENCE

(NONE)

## X. RELATED PROCEEDINGS APPENDIX

RELATED PROCEEDINGS

(NONE)